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10/735,602	12/12/2003	Hao-Jan Lin	JCLA10516	1741

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EXAMINER	
SULLIVAN, DANIEL M	
ART UNIT	PAPER NUMBER
1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/735,602	LIN ET AL.	
	Examiner	Art Unit	
	Daniel M. Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Non-Final Office Action is a reply to the Paper filed 7 September 2007 in response to the Non-Final Office Action mailed 12 June 2007. Claims 1-15 were considered in the 12 June Office Action. Claims 1 and 11 were amended in the 7 September Paper. Claims 1-15 are pending and under consideration.

Drawings

It is noted that the specification at page 5 includes a statement that the patent contains at least one drawing executed in color and that the USPTO will provide copies of color drawings upon request. However, no color drawings have been submitted to the Office. Applicant is reminded that color photographs and color drawings are not accepted unless a petition filed under 37 CFR 1.84(a)(2) is granted. Any such petition must be accompanied by the appropriate fee set forth in 37 CFR 1.17(h), three sets of color drawings or color photographs, as appropriate, and, unless already present, an amendment to include the following language as the first paragraph of the brief description of the drawings section of the specification:

> The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

Color photographs will be accepted if the conditions for accepting color drawings and black and white photographs have been satisfied. See 37 CFR 1.84(b)(2).

Response to Amendment and Arguments

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Rejection of claims 1-15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement as containing new matter is **withdrawn** in view of the claim amendments.

New Grounds

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 60/444,775, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application.

Specifically, the '775 application fails to disclose a method for delivering a biological material using a gene gun wherein the method requires that the gas provide to the pressurized chamber until the gas establishes a pressure "lower than 4 atm" as recited in the instant claims. In fact, the '775 application teaches practicing the method wherein the pressure is 100 psi (i.e., >6 atm). (Page 3, paragraph 2.) In view of this, the method presently claimed is not entitled to benefit of the '775 provisional application. Therefore, the claims are afforded an effective filing date of 12 December 2003.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6 and 15 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to

make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the invention and Breadth of the claims: The instant claim 6 is directed to a method of delivering a biological material using a gene gun wherein the biological material is "an immunogen for cancer immunotherapy". Claim 15 is directed to a method of delivering a biological material using a gene gun wherein the biological material is a nucleic acid and the nucleic acid "is used for gene therapy". As the claims limit the biological material to an explicitly recited intended use, enablement for the claims is evaluated based on the recited use. With regard to scope, the claims are generic to the use of any immunogen for cancer immunotherapy or the use of any nucleic acid for gene therapy. Therefore, as the first paragraph of section 112 requires that the scope of protection sought in a claim bear a reasonable correlation to the scope of enablement provided by the specification, it is incumbent upon the disclosure to teach the manner and process of making and using the claimed invention commensurate with the broad scope of to the use of any immunogen for cancer immunotherapy or the use of any nucleic acid for gene therapy.

State of the prior art and level of predictability in the art: The "predictability or lack thereof" in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there

is lack of predictability in the art. Accordingly, what is known in the art provides evidence as to the question of predictability.

The physiological art is recognized as unpredictable. (MPEP 2164.03.) In cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.

The relevant art is silent with regard to providing a therapeutically relevant immune response against a tumor by the method steps set forth in the claims. However, the art does teach that, at the time of filing, tumor vaccines were generally ineffective and that the therapeutic outcome of any given vaccination strategy was highly unpredictable.

Bodey et al. (2000) *Anticancer Res.* 20:2665-2676 flatly states, [t]he use of active specific immunotherapy (ASI) for cancer (cancer 'vaccines') is still in its scientific infancy despite several decades of clinical and basic research" (first full paragraph in the right column on page 2668). While acknowledging an occasional success in eliciting a response to "crude" vaccines and the isolation of tumor specific CTLs from solid tumors, draining lymphnodes, metastatic effusions, and peripheral blood of cancer patients, Bodey et al. teaches, "attempts at active specific immunotherapy using cancer vaccines have met with little success in clinical trials" (paragraph bridging the left and right columns on page 2668). Hersey et al. (1999) *Pharmacol. Ther.* 81:111-119 concurs with the teachings of Bodey et al. stating, "[a]lthough at

present there is much optimism associated with immunotherapy, it is an unfortunate fact that most patients are not cured by immune responses against their tumor and that most immunotherapeutic initiatives are not successful. When patients do respond, the clinician is usually unable to explain why that particular patient and not others responded" (first paragraph on page 111). Thus, Bodey et al. and Hersey et al. articulate the widely recognized view that the outcome of tumor vaccination in the treatment of any particular cancer is highly unpredictable and generally fails.

It is also recognized in the art that the causes underlying the generally poor outcome of cancer vaccination are manifold and incompletely understood. Platsoucas et al. (2003) Anticancer Res. 23:1969-1996 teaches, "certain major problems remain and need to be resolved in order to develop effective tumor vaccines. These problems emanate from the following mechanisms that the tumor cells are employing to avoid detection and destruction by the immune system: (i) Down-regulation of HLA class I expression on the surface of tumor cells; (ii) Down-regulation of tumor antigen expression or selection of negative tumor variants; (iii) Expression of naturally occurring altered peptide ligands by tumor cells; (iv) Lack of costimulatory molecules on tumor cells; (v)Production of immunosuppressive cytokines, such as TGF and IL-10; (vi) Induction of lymphocyte apoptosis by tumor cells using the Fas/Fas L pathway; (vii) Down-regulation or absence of CD3 zeta transcripts or protein in tumor-infiltrating lymphocytes, and others" (Abstract). Nawroki et al. (2001) Expert Opin. Biol. Ther. 1:193-204 concurs, stating, "[i]neffective immune response, in spite of the presence of well defined TA in many malignancies, is due to several escape mechanisms from immune recognition and exhaustion of immune system in advanced patients" (second full paragraph in the right column on page 200).

Given these teachings, one would anticipate that the ability of the claimed method to provide a therapeutic outcome for cancer using any given immunogen is highly unpredictable.

Likewise, at the time of filing, in vivo gene therapy utilizing the direct administration of recombinant nucleic acids, regardless of the mode of delivery (e.g., adenovirus, retrovirus, liposome), was considered to be highly unpredictable. Verma et al. states that, "[t]he Achilles heel of gene therapy is gene delivery...", and that, "most of the approaches suffer from poor efficiency of delivery and transient expression of the gene" (Verma et al. (1997) Nature Volume 389, page 239, column 3, paragraph 2). Marshall concurs, stating that, "difficulties in getting genes transferred efficiently to target cells- and getting them expressed- remain a nagging problem for the entire field", and that, "many problems must be solved before gene therapy will be useful for more than the rare application" (Marshall (1995) Science, Vol. 269, page 1054, column 3, paragraph 2, and page 1055, column 1).

Numerous factors complicate the gene therapy art which have not been shown to be overcome by routine experimentation. Eck et al. (1996) Goodman & Gilman's The Pharmacological Basis of Therapeutics, 9th Edition, Chapter 5, McGraw-Hill, NY, explains, "the delivery of exogenous DNA and its processing by target cells require the introduction of new pharmakokinetic paradigms beyond those that describe the conventional medicines in use today". Eck et al. teaches that with in vivo gene transfer, one must account for the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the in vivo consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA

produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically based on the vector used, the protein being produced, and the disease being treated (see Eck et al. bridging pages 81-82).

Also among the many factors that the art teaches affect efficient gene delivery and sustained gene expression are immune responses and the identity of the promoter used to drive gene expression. Verma et al. teaches that weak promoters produce only low levels of protein, and that only by using appropriate enhancer-promoter combinations can sustained levels of therapeutically effective protein expression be achieved (Verma et al., supra, page 240, column 2). Verma et al. further warns that, "...the search for such combinations is a case of trial and error for a given type of cell" (Verma et al., supra, page 240, bridging sentence of columns 2-3). The state of the art is such that no correlation exists between successful expression of a gene and a therapeutic result (Ross et al. Human gene Therapy, vol. 7, pages 1781-1790, September 1996, see page 1789, column 1, first paragraph). Thus, the art establishes that expectation for achieving a desired therapeutic effect in vivo by expressing a therapeutic gene using any of the expression constructs known in the art at the time of filing was extremely low.

In a more recent article, Rubanyi (2001) Mol. Aspects Med. 22:113-142 states, "[a]lthough the theoretical advantages of [human gene therapy] are undisputable, so far [human gene therapy] has not delivered the promised results: convincing clinical efficacy could not be demonstrated yet in most of the trials conducted so far..." (page 113, paragraph 1). Among the technical hurdles that Rubanyi teaches remain to be overcome are problems with gene delivery

vectors and improvement in gene expression control systems (see especially "3. Technical hurdles to be overcome in the future", beginning on page 116 and continued through page 125).

Beyond the technical barriers common to all gene therapy approaches, each disease to be treated using gene therapy presents a unique set of challenges that must be addressed individually. Rubanyi teaches, "each disease indication has its specific technical hurdles to overcome before gene therapy can become successful in the clinic" (bridging pages 131-132). In that regard, it is noted that Lavigne (2006) *Expert Opin. Emerging Drugs* (2006) 11:541-557 teaches that, as of 2006, only about 2% of the almost 1,000 gene therapy clinical trials approved worldwide have reached Phase III and that the number of successes is very small. (See especially the first paragraph of the "Background".)

In addition, it is noted that the record does not include a single example of an enabled gene therapy involving the administration of nucleic acids by a gene gun as recited in the instant claims. Lin et al. (2000) *Int. J. Dermatol.* (2000) 39:161-170 teaches, "As particle-mediated DNA delivery typically results in the short-term and inefficient expression of gene products *in vivo*, this approach has not been extensively investigated as yet, as a means of gene replacement." (First paragraph in the right column on page 163.) Although Lin et al. teaches that the gene gun has been useful in gene therapy research and postulates future applications in genetic vaccination, genetic pharmacology and cancer therapy, Lin et al. also teaches that the gene gun has limited applicability in conventional gene therapy. (Paragraph bridging page 167-168.)

Viewed as a whole, the art clearly evidences that successfully practicing the claimed method wherein the nucleic acid is used for gene therapy is highly unpredictable and must be empirically established for any given nucleic acid within the scope of the claims.

Amount of direction provided by the inventor and existence of working examples: The instant application provides detailed instruction as to how to deliver a nucleic acid into a cell using the disclosed gene gun apparatus. The application further demonstrates that the apparatus and methodology disclosed in the application can be used to express a reporter gene in the epidermis of a mouse (see especially paragraph 0056-0067). The applicant also demonstrates that the method can induce antibodies against EGFP in the transfected mice. (See especially paragraphs 0068-0073). However, the application provides no direction at all as to how to obtain an effective therapeutic response using the claimed method and fails to address the many sources of unpredictability in obtaining effective cancer immunotherapy and gene therapy.

Relative skill of those in the art and quantity of experimentation needed to make or use the invention: Although the relative level of skill in the art is high, the skilled artisan would not be able to practice the claimed invention such that the intended use recited in claims 6 and 15 could be achieved without undue experimentation. The art cited herein above clearly evidences that methods of cancer immunotherapy and gene therapy, in general, were at an early stage of development and highly unpredictable at the time the instant application was filed, and the record does not provide a single example of an enabled gene therapy involving the use of gene gun technology as presently claimed. In spite of this, the application seeks to claim methods that are generically drawn to the use of any immunogen for cancer immunotherapy or the use of any nucleic acid for gene therapy. However, given the broad scope of the claims, the unpredictable

state of the art and absence of any specific direction in the instant disclosure as to how to achieve an effective cancer immunotherapy or gene therapy by the claimed method, extending the teachings of the application such that it is enabled for the intended use recited in the claims would require undue trial and error experimentation. Therefore, the claims are properly rejected under 35 USC § 112, first paragraph, as lacking an enabling disclosure.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 15 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claim is indefinite in the recitation of "the nucleic acid". There is no antecedent basis for a nucleic acid in the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-5 and 7-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lin et al. (August, 2002) US Patent No. 6,436,709 B1 (previously made of record) in view of Tomalia et al. (January, 2002) US Pub. No. 2002/0013283 A1. (Please note that, in view of the 12 December 2003 filing date afforded the instant claims, the Lin et al. patent qualifies as prior art under 102(b). Therefore, the present rejection cannot be overcome under the provisions of 35 USC § 103(c).)

Independent claims 1 and 11 are directed to a method comprising the steps:

providing the gene gun comprising a pressurized chamber, a sprayer, a controller valve and a material delivery system;

placing a sample solution into the material delivery system, wherein the sample solution comprises at least the biological material;

triggering the gene gun and providing a gas through the controller valve to the pressurized chamber until the gas establishes a pressure lower than 4 atm;

releasing the sample solution from the material delivery system, so that the sample solution is accelerated by the gas in the pressurized chamber; and

discharging the sample solution out of the sprayer, wherein the sprayer includes a spray nozzle and a spray tube, and the spray nozzle comprises an interior contour, wherein the interior contour of the spray nozzle comprises a diverging part and a converging part-and a spray neck positioned between the diverging part and the converging part, wherein the sample solution is released from the material delivery system around the spray neck of the spray nozzle and is released in a direction perpendicular to a direction of the flow of the gas, and the spray tube is a diverging straight tube, so that a discharge speed of the sample solution is supersonic and the biological material is evenly injected into a target,

wherein the biological material is delivered without using metal particle carriers.

Claim 11 further recites that the gas is nitrogen gas or helium gas.

Claim 18 of Lin et al. also teaches a method comprising providing a gene gun comprising placing a sample comprising micro-particles in a suspension or dry powdery form into a material delivery system. As described in previous Office Actions, the powdery form can be construed as a "solution" according to the broadest reasonable interpretation of the limitation (see the Office Action mailed 18 October 2006, page 7, paragraph 1). In addition, absent evidence to the contrary, one of skill in the art would expect that when practicing the method of Lin et al. using a suspension of microparticles some small amount of the biological material attached to the microparticles would detach and go into solution. Therefore, practicing the method wherein some of the biological material is present in solution would be obvious to one of ordinary skill in

the art in view of the disclosure of Lin et al. The method of Lin et al. further comprises providing a gas—which can be nitrogen or helium (claim 22)—to the pressurized chamber until a preset pressure is reached, which might be less than 1 atm according to claim 18 of the Lin et al. patent. Finally, the method comprises spraying out the microparticles from the sprayer. Furthermore, Lin et al. discloses a gene gun having all of the properties recited for the gene gun of the instant claims. (See especially Figures 1-5 and the captions thereto.)

Thus, Lin et al. teaches a method comprising each of the limitations of the instant claims except that Lin et al. does not teach that the biological material is delivered without using metal particle carriers. (The only carrier particles explicitly contemplated by Lin et al. are tungsten and gold particles.)

Tomalia et al. teaches transfection particles useful for delivery of genetic material via particle bombardment methods (see throughout) and teaches, "In addition to metal particles, other suitable supports includes silica particles, alumina particles, and other solid supports having Lewis acid surface functionality. Also, it has been determined that dendritic polymers conjugated to genetic materials, without any metals or other support materials conjugated thereto may also be usefully employed as gene transfection particles in particle bombardment methods." (Paragraph 0010.)

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Lin et al. by substituting non-metal particles such as silica or dendritic polymers for the tungsten or gold particles explicitly taught by Tomalia et al. In *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007), the Supreme Court particularly emphasized "the need for caution in granting a patent based on a combination of elements found

in the prior art," (*Id.* At 1395) and discussed circumstances in which a patent might be determined to be obvious. Importantly, the Supreme Court reaffirmed principles based on it precedent that "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." (*Id.* At 1395.)

In the instant case, Lin et al. teaches a method which differs from the method presently claimed only in that the instant claims require that the solution used to deliver the biological material be delivered without using metal particle carriers. However, the teachings of Tomalia et al. demonstrate that it was known in the art at the time the instant invention was made that non-metal carriers such as silica or dendritic polymers could be used in particle bombardment methods of delivering biological materials into cells. One of ordinary skill in the art could have substituted non-metal particle carriers as taught by Tomalia et al. for the metal particle carriers used in the method of Lin et al. Furthermore, substitution of the non-metal carriers would have predictably resulted in transfer of biological material into cells, as Tomalia et al. teaches that the non-metal particles are suitable supports for particle bombardment and it has been determined that dendritic polymers conjugated to genetic materials may also be used as gene transfection particles in particle bombardment methods in the absence of metals or other support materials.

In view of the foregoing, the invention of independent claims 1 and 11, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made. Furthermore, the limitations of the instant dependent claims are also found in the cited art. In paragraph Tomalia et al. teaches that viruses, viral fragments, DNA, proteins, etc. can be delivered using the carriers disclosed therein according to the requirements of claims 2-5 and 15 (paragraph 0012; note that the recitation of an intended use does not distinguish the nucleic acid

of claim 15 from prior art nucleic acids.) Lin et al. teaches that the microparticles are accelerated to a velocity of 200-300 m/s according to the limitations of claim 7 and 12 (see especially column 3, lines 25-26). Lin et al. teaches, "According to the theory of aerodynamics, as the pressure difference between the internal and external of the spray nozzle is greater than 0.9 atm, supersonic flow is generated." (column 3, lines 29-32) and claims the method wherein the pressure is less than 1 atm (claim 18). These teachings render obvious a pressure of about 1 atm according to the limitations of claims 8 and 13. Lin et al. also teaches a gene gun having the dimensions recited in the instant claims 9 and 14 (see especially column 6, lines 35-45) and as described above, Lin et al. teaches that the gas used might include helium or nitrogen gas according to the limitations of claim 10 (claim 22).

Thus, the method of the instant claims, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claims are properly rejected under 35 USC § 103(a) as obvious over the art of record.

Claims 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lin et al. (*supra*) in view of Tomalia et al. (*supra*), as applied to claim 1 herein above, and further in view of Wu et al. (2001) WO 01/29233 A2.

Claim 6 is directed to the method of claim 1 wherein the biological material is an immunogen for cancer immunotherapy. It is noted that the intended use is considered limiting only insofar as the immunogen must have the capacity to provide an immune response against a cancer cell. The art is not required to enable the intended use recited in the claim.

As described above, the method of claim 1, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made in view of the teachings of Lin et al. and Tomalia et al. Neither Lin et al. nor Tomalia et al. specify the properties of the nucleic acids or proteins disclosed therein. Wu et al. teaches the use of a gene gun to deliver an immunogen capable of eliciting an immune response against a tumor in mouse. (See especially Figures 3-6 and the captions thereto.)

It would have been obvious to one of ordinary skill in the art at the time the invention was made to include a nucleic acid encoding a tumor antigen among those delivered according to the method of Lin et al. in view of Tomalia et al. In *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007), the Supreme Court particularly emphasized "the need for caution in granting a patent based on a combination of elements found in the prior art," (*Id.* At 1395) and discussed circumstances in which a patent might be determined to be obvious. Importantly, the Supreme Court reaffirmed principles based on it precedent that "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." (*Id.* At 1395.)

In the instant case, the Lin et al. in view of Tomalia et al. teaches a method comprising all of the elements of the method presently claimed except for an explicit teaching that the method can be used to deliver an immunogen capable of eliciting an immune response against a cancer cell. However, the teachings of Wu et al. demonstrate that it was known in the art at the time the invention was made that nucleic acids encoding immunogens capable of eliciting an immune response against cancer cells could be delivered using a gene gun. In view of the high level of skill in the art evidenced by the highly technical nature of the cited publications, one of ordinary

skill in the art could have combined the elements of the prior art according to the requirements of the instant claims by known methods and, in that combination, each element merely would have performed the same function as it did separately. Furthermore, one would have expected that the combination would have predictably resulted in expression of the immunogen.

Thus, all of the elements of claim 6 were known to one of ordinary skill in the art at the time the invention was made and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions and the combination would have yielded nothing more than predictable results to one of ordinary skill in the art at the time of invention. Therefore, the claimed invention, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M. Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Friday 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D. can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Art Unit 1636